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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/891,138
Filing Date: June 25, 2001
Appellant(s): LIN ET AL.

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 03/14/2005.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

§ 1010

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

The rejection of claims 3, 6, 7, 13, 30, and 31 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Prior Art of Record*

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) *Grounds of Rejection*

The rejection of claims 6,7, and claims 30 and 31 as they relate to claims 6 and 7, as failing to meet the written description requirement under 35 U.S.C. § 112, first paragraph is hereby withdrawn. Upon reconsideration, the Examiner holds that the disclosed sequences provide written description of an isolated nucleic acid encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:2 and a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, to which claims 6 and 7 are drawn without recitation of an activity.

The following ground(s) of rejection are applicable to the appealed claims:

Claims 3, 6, 7, 13, 30, and 31 stand rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility. The detailed explanations of the scientific basis for holding that the claimed invention does not have a well-established utility and that the specification as filed does not establish a specific or substantial utility have been made of record (see Non-Final Rejection, 04/15/2003, sections 5-7) and are summarized as follows. The pending claims are drawn to an isolated nucleic acid encoding a polypeptide comprising at least 200 contiguous amino acids of a polypeptide referred to as TGR18. The specification discloses that the amino acid sequence of TGR18 has characteristics of a G-protein coupled receptor (GPCR). There are no well-established utilities for newly discovered biological molecules. The fact that TGR18 is a GPCR is not sufficient to infer specific utility because the superfamily of GPCRs includes over 5000 genes, which encode receptors with diverse functions, different activating ligands, different second messenger systems, and different roles in physiology. While all GPCRs share a common

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structural theme of having seven transmembrane domains, their amino acids sequences are highly divergent, even among subfamilies with similar functions, so it is not possible to infer activity or function from amino acid sequence alone. The specification shows that TGR18 is expressed in the kidney but does not indicate what it does there or what effect activation or inhibition of TGR18 signaling would have on kidney function. There are no working examples of a functional TGR18, and no ligand for the receptor is disclosed. All assertions of utility are nonspecific, such as can be made for any coding nucleic acid or, at best, generic to the class of G-protein coupled receptors. The asserted utilities are not substantial because the disclosure did not establish that the claimed GPCR had an activity that linked it to a physiological process or state.

Claims 3, 6, 7, 13, 30, and 31 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim 3, and claims 30 and 31 as they relate to claim 3, stand further rejected under 35 U.S.C. § 112, first paragraph, because the specification as filed fails to enable a polypeptide comprising as few as 200 contiguous amino acids of SEQ ID NO:2 as recited in claim 3. The basis for this rejection was given in section 20 of the Final Rejection as follows:

GPCRs or Serpentine receptors have by definition 7 transmembrane domains. Each transmembrane domain consists of an α -helix, which is a minimum of 20 amino acids, connecting each TMD is a open formation polypeptide chain of about 10 amino acids (forming both extracellular and intracellular loops). Therefore at minimum a true GPCR would have 230 residues. This excludes any binding domains, secondary messenger docking domains, catalytic domains, and the like. Therefore it is physically impossible to have a GPCR with only 25 amino acids, or 100, or 200 (references omitted).

Thus, even if one accepts transduction of an increase in intracellular calcium as an activity (albeit non-specific and not supported by the specification as filed) of TGR18, claim 3 additionally lacks enablement because it is drawn to embodiments for which there is ample reason to believe would not be functional. Therefore, it is incumbent upon the applicant to provide guidance in overcoming the obstacles that would be readily apparent to one of skill in the art. Such guidance is not found in the specification and therefore claim 3 and its dependent claims are not enabled.

Claim 13, and claims 30 and 31 as they relate to claim 13, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection has been made of record in the Office Actions mailed on 04/15/2003 and 02/20/2004, summarized as follows. Claim 13 is drawn to an isolated nucleic acid encoding a G-protein coupled receptor that transduces an increase in intracellular calcium, wherein the nucleic acid encodes a polypeptide comprising 95% or greater amino acid identity to the amino acid sequence of SEQ ID NO: 2. Applicant is claiming further sequence derivations of an invention without utility that is not enabled. Only isolated nucleic acids comprising the sequence set forth in SEQ ID NO: 1, encoding a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. With the exception of SEQ ID NO: 1 and SEQ ID NO: 2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires

more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. The instant claims recite a percent identity, which is an insufficient structure parameter and one with no functional value, with a disclosed sequence with no utility that is not enabled and thus does not satisfy the written description requirement.

(11) Response to Argument

Claim Rejections - 35 USC § 101

Beginning at p.5 Appellant attempts to demonstrate that the claimed invention satisfies the requirement for utility under 35 U.S.C. § 101. The argument begins on p. 6 with citations of the MPEP and case law regarding standards to address utility. The referenced sections of the MPEP point out that rejection for lack of utility should not be made if an applicant has asserted a specific, substantial, and credible utility and that a detailed explanation, including the scientific basis, must be given for any utility rejection.

Appellant's citations of *In re Langer* and *In re Gaubert* (middle page 6) are noted; however their relevance is unclear because they are directed toward cases where a specific assertion of utility has been made. The Examiner has not questioned the objective truth of any statement of utility but rather holds that the disclosure as originally filed did not assert a utility that is specific or substantial.

On p.7, first paragraph, Appellant asserts, "The invention satisfies utility under 35 U.S.C. § 101 because the identification of TGR18 nucleic acids permits one of skill in the art to analyze modulators of TGR18." This asserted utility actually encompasses several utilities such as use of the invention for "analysis, characterization", screening for ligands for the encoded polypeptide,

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and screening for compounds that regulate TGR18 expression. These asserted utilities have been addressed in the Non-Final Rejection, 04/15/2003, specifically sections 6c, 6d, and 6i, portions of which are reiterated here (asserted utilities in italics).

c. The isolated nucleic acid (SEQ ID NO: 1) can be used to make a polypeptide (SEQ ID NO: 2) for analysis, characterization, or therapeutic uses: This asserted utility is not substantial nor specific. In recombinantly expressing a polypeptide, the polynucleotide is transfected into a host cell and then the protein is recovered. However, the instant specification does not disclose any known function for the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 1. In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

d. The polypeptide (SEQ ID NO: 2) encoded by SEQ ID NO: 1 can be used to screen for a ligand: The asserted utility is also not specific, since all receptors can be used to screen for ligands.

i. The claimed nucleic acid molecules can be used in assays for drug screening to identify compounds that modulate secreted protein nucleic acid expression: This asserted utility is also not substantial. In such assays, compounds are screened for their ability to up-regulate or down-regulate expression of the nucleic acid molecule. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 1 expression levels or forms (i.e., mutations). Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial.

In short, TGR18 nucleic acids, by themselves, do not permit one of skill in the art to analyze modulators of TGR18. One first needs an assay of TGR18 activity. The specification provides generic descriptions of activities that GPCR are known to have, but does not indicate which one is specific to TGR18. Even if one knew how to measure TGR18 activity, screening for modulators would not be a substantial utility because, in the absence of a nexus between TGR18 and a physiological process or disease state, one would not know what to do with the

modulators once they were found. Screening for substances with no utility cannot be a substantial utility.

The remainder of p. 7 of Appellant's Brief is a recapitulation of Examiner's prior arguments to which Appellant responds on p.8-10. Appellant particularly draws attention to the Examiner's prior conclusion that Lin declaration I does not establish a specific utility (second paragraph of p.7) and asserts on p. 8 (third paragraph) that Lin Declaration I demonstrates that TGR18 has a known GPCR activity, i.e., it transduces an increase in intracellular calcium. It has been pointed out (section 10, page 3 of the Final Office Action, 02/20/2004) that many GPCRs modulate changes in intracellular calcium when generally stimulated. This would be expected especially in an experimental system where a GPCR is given an opportunity to interact with promiscuous G-proteins as described in the specification at p.42, lines 26-30. Therefore, although the data presented in the Lin Declaration I shows that the claimed GPCR is an active receptor, it does not reveal anything specific about the receptor.

On p.8, second paragraph, Appellant asserts: "The specification further teaches that...TGR18 can participate in the modulation of cellular function in cells, for example kidney cells, in which it is expressed (see, e.g., page 51, lines 31-34)." The cited sentence reads thusly, "For example, the activity of GPCRs (e.g., TGR18) that are expressed in a particular cell type (e.g., kidney cells), can be used to modulate cellular function (e.g., responsiveness to extracellular signals), thereby specifically modulating the function of the cells of that type in a patient." This is clearly not a "teaching" but rather it is a generic statement that includes TGR18 as a speculative example. Furthermore, it is not specific as "modulate" can indicate any kind of change; every expressed protein modulates cellular function in some way. Appellant further

states “the specification also discloses that a GPCR that is predominantly expressed in the kidney can play a role in renal disease, e.g. hypertension (see, e.g., page 52, lines 2-6)”. The same lines from the specification are cited again on page 10 (“Specific utility”) to support the assertion that the present application discloses that TGR18 plays a role a disease condition (e.g., hypertension) that correlates with a “biological activity” i.e., GPCR activity. The cited sentence reads thusly, “For example, kidney-specific GPCRs will likely result in any of a number of nephrotic conditions or diseases...” Again, this is not a specific teaching about TGR18, but a generic statement about GPCRs. Furthermore, the speculative phrase “will likely result in” is a far cry from a disclosure that “TGR18 plays a role”.

On p.9, Appellant addresses the He *et al.* publication in which TGR18 was shown mediate an increase in intracellular calcium in response to succinic acid as ligand. Appellant further points out significant findings discussed in the He *et al.* paper, specifically that succinic acid was known to regulate re-absorption of phosphate and glucose into the proximal tubule, and to stimulate renin release. Further, He *et al.* showed that TGR18 was required for succinic acid-induced hypertension in mice. Thus, the He *et al.* paper provides some of the information that had been lacking in Lin Declaration I concerning the biological significance of succinic acid in the kidney. Had this information been included in the original disclosure, a strong argument for utility of TGR18 might have been established. However, all of these pertinent facts were learned after filing. A GPCR that transduces an increase in intracellular calium, with succinic acid as its ligand, is not supported by the specification as filed. The terms “succinic acid” or “succinate” do not appear in the disclosure. The “teachings” of the application as filed are so general that they would have been equally valid if subsequently TGR18 had been shown to be activated by any

ligand, with any of several intracellular pathways activated, in any part of the kidney, with the response being either raising or lowering of blood pressure.

At the bottom of p. 10, Appellant takes issue with the Examiner's position that the asserted utility is not substantial because more research is required to determine how to use the claimed [invention]. The correctness of the Examiner's position is proven by the record. Indeed, more research was required to determine how to use the claimed invention. To wit, He *et al.*

On p. 11, Appellant cites *Brenner v. Manson* with regard to the importance of the policy of encouraging early disclosure. It is important to note that while giving due consideration to this important matter, the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966).

And,

"Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

The asserted utilities "valuable probes for the identification of particular cell types", "isolation of specific modulators of GPCR activity" (specification p. 6, lines 23-29); "to identify diseases, mutations, and traits caused by and associated with the GPCRs" (p. 7, lines 5-6) amount to "use testing" of the claimed invention. The application as filed does not represent a successful conclusion, but rather it is a hopeful beginning of a search.

Next, Appellant asserts that the present case is analogous to *Nelson v Bowler*. To summarize, *Nelson v Bowler* was an interference proceeding. The issue was whether Nelson, the junior party, had established utility prior to Bowler's filing date, *i.e.* also before Nelson's own filing date. The inventions at issue were prostaglandin compounds about which a great deal was previously known as they had been purified from natural sources and tested thoroughly in biological systems. The cited quote shows that the CCPA decided that tests showing pharmacological activity of the synthetic compounds were sufficient to establish patentable utility even though no specific therapeutic use for the compounds was established.

Appellant asserts that the present case is analogous to *Nelson v Bowler* because TGR18 has a physiological function in the kidney and compounds capable of modulating TGR18 are useful as agents for regulating its function. However, there are several differences in the respective fact patterns that indicate that the present case is not analogous to *Nelson v Bowler*. First, unlike prostaglandins F₂ and F_{2a}, TGR18 is not a synthetic copy of a naturally occurring substance with known physiological activities. Instead, TGR18 is a newly described member of a gene family that has over a thousand members. The present specification as filed did not disclose a physiological function for TGR18. The skilled artisan would not know how to find compounds capable of modulating TGR18, without first doing research, and then the artisan would have to do still more research to find out how modulating TGR18 activity affects kidney function. *Then* the skilled artisan would be able to decide whether TRG18 or its modulators are useful. This points to another major difference in the fact patterns of *Nelson v Bowler* and the present case, specifically, the timing involved. In *Nelson v Bowler*, the CCPA ruled that Nelson had achieved

reduction to practice prior to either filing date. In the present case, it appears that reduction to practice occurred some time between the filing date and the publication of He *et al.*

Claim Rejections - 35 USC § 112

Appellant has responded to the rejection of Claim 3, and claims 30 and 31 as they relate to claim 3, under 35 U.S.C. § 112, first paragraph, enablement, by asserting (p. 15, second paragraph) that the specification teaches chimeric molecules in which domains or other regions of the claimed sequences are used in the context of a heterologous protein that have activity. The section of the specification cited as support for this assertion, p. 40, lines 11-25, reads in pertinent part:

Either a GPCR or a domain thereof can be covalently linked to a heterologous protein to create a chimeric protein used in the assays described herein... Signal transduction can also be examined in vitro with soluble or solid state reactions, using a chimeric molecule such as an extracellular domain of a receptor covalently linked to a heterologous signal transduction domain, or a heterologous extracellular domain covalently linked to the transmembrane and or cytoplasmic domain of a receptor.

This “teaching” is entirely prophetic, as the specification offers no guidance as to which portions of the claimed sequence would be included in a functional embodiment of the proposed chimeric protein. No working examples are provided. No references to the successful application of this approach to other GPCR are cited. Before practicing this approach, the skilled artisan would first have to develop an assay for TGR18 activity (not provided in specification), discover a ligand that can reliably activate the intact TGR18 receptor (also not provided), and then undertake systematic characterization of the various domains.

In the argument regarding enablement on pp. 14-17 of the Appeal Brief, Appellant generally argues that one of skill in the art could reasonably expect to use various combinations

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of knowledge of SEQ ID NO:2, general knowledge of GPCR domains, related sequences disclosed in U.S. Patent No. 5,871,963 , sequence alignment algorithms, together with the knowledge that TGR18 has an activity of transducing an increase in intracellular calcium, to identify active variants. This line of reasoning is essentially the same as have been made in the response to the first Non-Final rejection, in which Appellant argues that the specification provides guidance to make the claimed sequences based on structural properties and guidance for performing assays to assess the function of the sequences. This argument has been previously addressed in the Final Rejection, section 25, and is reiterated herein:

“the claims as currently presented constitute an invitation to experiment. Insufficient guidance is presented to support the undertaking of screening, isolating, and characterizing all the fragments and sequence derivatives currently claimed. The Applicant provides only prophetic consideration of what should be done, lists a battery of assays available to the artisan, and suggests possible results. Further since SEQ ID NO: 1 fails to meet the utility requirement as extensive research is required to first characterize SEQ ID NO: 1 before under taking extensive experimentation to screen, isolate, and characterize all of the fragments and sequence variants claimed.”

While the above rejection was directed to a larger set of claims, some of which have now been amended or cancelled, the reasoning still applies to claim 3.

With regard to the rejection of claim 13, and claims 30 and 31 as they relate to claim 13, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification, Appellant’s argument (pp. 21-22) centers on the relationship of the present claims to Example 14 of the “Revised Interim Written Description Guidelines”. Appellant points out that, in Example 14, a disclosure is held to provide adequate written description for claims to a protein with 95% sequence identity to a sequence when the reference protein has a known function and the specification provides an assay for protein activity. Appellant then asserts that

these conditions are met in the instant case because TGR18 has function, the sequences of TGR18 “do not exist in a context devoid of the knowledge of similar sequences”, conserved structural features of GPCRs are known, and examples of conservative substitutions are given in the specification.

The disclosure as filed, however, does not provide a combination of structural features coupled with a known or disclosed correlation between function and structure so as to provide adequate written description. First, contrary to Appellant’s assertions on p. 21 (third paragraph), neither a disclosure of a specific function nor an assay for TGR18 activity were provided in the specification; only generic descriptions of GPCR functions and activities are provided. Then, even if one were to guess correctly that TGR18 would transduce an increase in intracellular calcium in response to succinate, the specification gives no guidance as to how the reference sequence may be modified while still retaining this activity. It is indeed true that structural features common to all GPCRs are known (sentence bridging p.21-p.22), but the state of the art does not teach a consensus for residues within the general structure of GPCRs that are required for calcium signaling, even when the related sequences such as those disclosed in U.S. Patent No. 5,871,963 (cited by Appellant on p. 20 and alluded to on p. 21) are taken into account, That is, sequence information alone would not be usable to predict which positions in TGR18 might be changed without a loss of function.

For the above reasons, it is believed that the rejections should be sustained.

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Respectfully submitted,

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May 24, 2005

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